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Award Number: DAMD17-01-1-0325

TITLE: Influence of Radiotherapy and Tamoxifen on Contralateral Cancer Risk in Women with Hereditary Breast Cancer

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REPORT DATE: July 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 2004	Annual (1 July 2003 - 30 June 2004)

4. TITLE AND SUBTITLE
Influence of Radiotherapy and Tamoxifen on Contralateral Cancer Risk in Women with Hereditary Breast Cancer

5. FUNDING NUMBERS
DAMD17-01-1-0325

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*:

Women with breast cancer arising as a consequence of germline mutations in *BRCA1* or *BRCA2* are at significant risk of contralateral breast cancer (CBC). Examination of factors influencing contralateral risk will provide insight into prevention strategies for unaffected women with BRCA mutations. To evaluate CBC risk factors, the funded study was designed to assess the impact of tamoxifen and radiotherapy on CBC risk. Records from a total of 874 Ashkenazi women with breast cancer diagnosed between 1990 and 1996 were reviewed to expand the initial cohort of 305 women treated between 1980 and 1990. Changes in medical record storage and HIPAA privacy regulations prevented the gathering of required basic clinical and/or follow-up information for 75% of patients diagnosed between 1990 and 1992, and for approximately 20% of patients diagnosed between 1992 and 1996. The loss of the patients from the data set introduced a possible survival bias, and thus alternative methods of addressing the study goals were sought. Specifically, concatenation of the original 1980-1990 data-set with a similar ascertainment from another institution was performed, suggesting a 53% contralateral risk reduction with adjuvant tamoxifen, and 103 clinically-ascertained patients were analyzed. The clinical ascertainment did not support a benefit from tamoxifen.(199 words)

14. SUBJECT TERMS	15. NUMBER OF PAGES
BRCA1, BRCA2, hereditary breast cancer, radiotherapy, tamoxifen	9
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction

Although women with *BRCA1* or *BRCA2* mutations constitute a small minority of breast cancer patients overall, in some populations (e.g. Ashkenazi Jewish women with breast cancer before age 50), an appreciable proportion of cancers are *BRCA*-related. Women with germline mutations are at substantially increased risk of breast cancer, both *de novo* and contralaterally after a first cancer diagnosis. The study of factors influencing the development of contralateral cancer in such women may provide important clues as to the risks and benefits of certain prevention strategies for unaffected individuals. Exposures that promote the development of contralateral disease should likely be avoided by both affected and unaffected heterozygotes, while interventions that reduce contralateral risk are obvious candidates for deployment in the primary prevention arena. Unfortunately, survival and selection biases may confound the study of variables modulating contralateral risk in prevalent groups of women with *BRCA* mutations, who are usually identified through familial cancer clinics. The present study, employing a retrospective anonymized design, was intended to circumvent those biases and allow the collection of a relatively unselected group of women with *BRCA* mutations for the examination of factors influencing contralateral risk.

Body

To accomplish the aims of the funded project, we extended our previous work examining outcomes in Ashkenazi women with invasive breast cancer. In our original publication, performed without DOD funding, we reported local control and systemic outcomes in Ashkenazi women with breast cancer treated at our institution with lumpectomy and adjuvant radiotherapy between 1980 and 1990, comparing the clinical outcomes of women with or without germline founder mutations in *BRCA1* or *BRCA2*. A retrospective, anonymized design was employed to address the difficult human subjects issues relevant to germline predisposition research. Once notice was received of funding for extension of the project, we first reviewed the initial cohort and determined the impact of tamoxifen on contralateral cancer risk among the mutation carriers in that study. There were 25 mutation carriers for whom tamoxifen use was known. There was 1 metachronous contralateral cancer among 5 mutation carriers taking tamoxifen, and 6 among the 20 carriers not taking tamoxifen (HR 0.57[95% CI: 0.07-4.57; P=0.6]).These data were presented at the 2002 Era of Hope meeting.[1]

Subsequently, local IRB and Department of Defense HSRRB approval was obtained to allow records review and tissue acquisition from Ashkenazi women receiving treatment (either lumpectomy and radiation, or mastectomy with or without adjuvant radiation) for invasive breast cancer between 1990 and 1995 at Memorial Sloan-Kettering. Final approval to initiate this expansion was received at the end of August 2001, and contracting was completed by 30 October of that year. In accordance with the Statement of Work agreed upon, from October 2001-March 2002, institution databases were reviewed to identify women diagnosed with invasive breast cancer in that interval from 1990-1992. Hospital registration databases were cross-referenced to identify women of self-reported Jewish religious preference (an effective surrogate for Ashkenazi ancestry in our patient population). Over 800 Jewish women were treated for invasive breast cancer at Memorial Sloan-Kettering in 1990, 1991, and the first half of 1992. Of those, 422 had pathology material available, the remainder having received primary surgical therapy elsewhere. Unfortunately, medical records were only retrievable for 25% of these patients. It was found that, after our institution converted to an electronic medical record system in 1998, it became extremely difficult to access medical records for women who had become inactive patients. Women who were survivors were more likely to have active records, which were retrievable. This raised concerns that the ascertainment would become subject to a "survivor bias." Follow-up data were also inconsistently available as many of the subjects were not considered "analytic cases" by the hospital tumor registry, their initial biopsy diagnosis having been made elsewhere before referral to our institution for definitive treatment. Traditional means of obtaining follow-up on such patients, such as calling their local physicians, are now prohibited by HIPAA regulation.

In response to the difficulties encountered in retrieving records from 1990-1992, the ascertainment was expanded, and records for women diagnosed between 1992 and 1996 were reviewed. Based upon this expansion, as described in the November 2003 Annual Report, we identified 452 additional women with pathology material theoretically available for genotyping. We anticipated beginning genotyping in February 2004, and completing the data analysis by June 2004. Unfortunately, similar problems with follow-up were encountered with the expanded data set. Recent follow-up data (within 4 years) were unobtainable for approximately 78 patients (17%), with critical treatment information being found to be missing in a substantially greater number of cases. Again, recently evaluated patients are, by definition, survivors, were more likely to have retrievable records and the lack of follow-up information of a substantial proportion of the remaining cases posed a very risk of introducing a survival bias into the analysis. Records have been requested on several occasions from the institutional archival

retrieval service, without response as yet.

The difficulties completing the clinical follow-up resulted in falling behind the schedule in the project Statement of Work. We have requested a 1-year no-cost extension to this project to allow us to further pursue the relevant records and follow-up information prior to anonymizing and performing the genotyping. In addition, we are investigating extending the ascertainment even further forward (up to 1998 or even 2000) in order to achieve the goal of 1000 cases for genotyping. Results obtained from anonymizing and genotyping the currently available data set, as it stands, are likely to be confounded by survival bias, and thus suboptimal for resolution of the study questions. If the problem of incomplete follow-up cannot be resolved, then the analysis will proceed, and all cases, with or without follow-up, will be genotyped to demonstrate that mutation prevalence in the two groups does not differ. If this is the case, then we will conclude that the outcomes of the group with follow-up are likely to reflect the experience of mutation carriers who are lost to follow-up.

Given the difficulties encountered in developing the cohort for anonymized study, two different approaches have been taken to address the study goal of identifying factors associated with contralateral cancer risk in *BRCA* mutation carriers, and particularly the potential benefit of tamoxifen. First, data from our first anonymized series were combined with a similar series from the Jewish General Hospital in Montreal. The combined series comprised 496 women who underwent breast conserving treatment for 520 breast cancers. There were a total of 56 mutation carriers. The relative risk of contralateral breast cancer in mutation carriers receiving tamoxifen, compared to those not receiving tamoxifen, was 0.47 (95% C.I. 0.14-1.59; P= 0.23).[2] DOD support was specifically acknowledged in this publication. Second, the clinic-based ascertainment of affected *BRCA* mutation carriers was reviewed and clinical data extracted to determine outcomes in women undergoing breast-conserving therapy. In this clinic-based ascertainment, which does not significantly overlap with the previous Ashkenazi ascertainment or with the un-selected 1990-1996 ascertainment, there were 103 carriers who were initially treated with breast-conserving intent for 115 breast cancers. There were no statistically significant differences in the 5- or 10-year risk of contralateral breast cancer between the 37 mutation carriers who received tamoxifen for their index breast cancer and the 64 women who did not. Tamoxifen status was unknown for 2 women. These results were presented at the 2004 Annual Meeting of the American Society of Clinical Oncology in New Orleans, LA.[3] A manuscript has been submitted, and DOD support specifically acknowledged.

Key Research Accomplishments

- Reviewed initial Ashkenazi breast conservation cohort to determine impact of tamoxifen in that group. Abstract presented at Era of Hope meeting in Orlando, Florida in September 2002.
- Identified 800 Ashkenazi women with breast cancer treated at MSKCC between 1990 and 1992, 422 of who had pathology material theoretically available for genotyping, but only 25% of who had sufficient clinical information and follow-up available for potential inclusion in cohort. Available data extracted and clinical data reviewed.
- Identified 454 additional Ashkenazi women with breast cancer treated at MSKCC between 1992 and 1996 with pathology material theoretically available. Of this group, clinical information and/or follow-up information was unobtainable for 17%. Available records extracted and data reviewed.
- Completed and published a combined analysis of initial 1980-1990 Ashkenazi cohort and a similar ascertainment from Jewish General Hospital, Montreal, Canada to determine impact of tamoxifen on contralateral cancer risk. DOD support recognized.
- Evaluated factors associated with contralateral breast cancer risk (particularly tamoxifen) in clinic-based ascertainment of women identified as mutation carriers by MSKCC Clinical Genetics Service between 1992 and 2003, and reported results at ASCO. DOD support will be recognized in publication.

Reportable Outcomes

The results of the impact of tamoxifen on CBC risk in the MSKCC dataset were presented at the 2002 Era of Hope meeting in Orlando. In this dataset, the RR of contralateral cancer among mutation carriers using tamoxifen was 0.57, but statistical significance was not reached.

The impact of tamoxifen in a combined series of un-selected Ashkenazi patients (MSKCC and Jewish General Hospital, Montreal) was published in *Breast Cancer Research* in 2004. DOD support was recognized. In the combined series, relative risk of contralateral breast cancer in mutation carriers receiving tamoxifen, compared to those not receiving tamoxifen, was 0.47 (95% C.I. 0.14-1.59; P= 0.23).

The impact of tamoxifen on contralateral cancer risk was evaluated

in a non-overlapping clinic-based ascertainment of 103 *BRCA* mutation carriers. In these women, tamoxifen did not significantly reduce contralateral risk at either 5 or 10 years (T vs. No T 10.6 vs. 14.4 % at 5 years and 34.8 vs 40.8% at 10 years). These data were presented at the Annual Meeting of ASCO in New Orleans in 2004, and the manuscript has been submitted to *Cancer* for review.

Conclusions

The goal of the project was to evaluate the impact of tamoxifen and radiotherapy on contralateral breast cancer risk in women with germline mutations in *BRCA1* and *BRCA2*. Previous studies have been confounded by potential survival bias, and an anonymized retrospective design was therefore proposed. The implementation of this design has been severely hampered by difficulty retrieving clinical data caused by changes in the medical record management practices, and specifically conversion to an electronic medical record. In addition, recent follow-up information on patients diagnosed over a decade ago, but no longer followed at MSK, has become very difficult due to HIPAA regulations which restrict external physicians from providing follow-up information. This has raised the possibility of introduction of the same survival bias that the anonymized design is intended to circumvent, as only survivors have recent follow-up at our institution. These difficulties have lead the project to fall behind schedule, and completion of clinical data analysis and follow-up is not yet complete at the end of the funding period. A no-cost extension has been requested to allow completion of this follow-up, and genotyping of the available patients with appropriate statistical correction for missing follow-up being made at the analytic stage.

Given the difficulties encountered in realizing the original anonymized design, the specific aims of the project were addressed through alternative means. First, a collaboration was established with Jewish General Hospital (Dr. William Foulkes), and data from the two similar retrospective anonymized cohorts were combined. This allowed an approximate doubling of the number of mutation carriers available for study, which continued to suggest a benefit in terms of contralateral risk reduction from tamoxifen, although, even in the expanded data-set, the numbers were insufficient to achieve statistical significance. In addition, a non-overlapping clinic-based cohort was analyzed, which failed to suggest a similar tamoxifen benefit. This analysis may, however, been confounded by a propensity for women with contralateral cancer to present for genetic testing, which could have obscured a benefit of tamoxifen.

In conclusion, the work performed under this contract has continued to support a benefit from tamoxifen in reducing contralateral breast cancer risk in women who receive the drug for their index

breast cancer, but the number of carriers available for study who have received the agent remains too small to prove a benefit. The specific aims were addressed using alternative approaches when it became evident that the originally planned approach was being delayed by unanticipated administrative and regulatory complications. We have requested a no-cost extension to confirm these findings by continuing the development of the unselected cohort.

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